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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	4	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	5	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	6	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	7	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS	8	JAN 30	Saved answer limit increased
NEWS	9	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	10	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS	11	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	12	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	13	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS	14	FEB 28	TOXCENTER reloaded with enhancements
NEWS	15	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS	16	MAR 01	INSPEC reloaded and enhanced
NEWS	17	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	18	MAR 08	X.25 communication option no longer available after June 2006
NEWS	19	MAR 22	EMBASE is now updated on a daily basis
NEWS	20	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	21	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	22	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS	23	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS	24	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS	25	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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FILE 'BIOSIS' ENTERED AT 11:02:15 ON 25 APR 2006
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=> oncolytic or oncolysis
L1        2263 ONCOLYTIC OR ONCOLYSIS

=> reovirus
L2        5743 REOVIRUS

=> l1 and l2
L3          95 L1 AND L2

=> fluorouracil
L4       43156 FLUOROURACIL

=> mitomycin
L5       27736 MITOMYCIN

=> methothrexate
L6          37 METHOTHREXATE

=> Hydroxyruea
L7           3 HYDROXYRUEA

=> cyclophosphasmid
L8           0 CYCLOPHOSPHASMID

=> cyclophosphamide
L9       57023 CYCLOPHOSPHAMIDE

=> dacarbazine
L10       3183 DACARBAZINE

=> mitoxantrone
L11       7894 MITOXANTRONE

=> anthracyclins
L12         95 ANTHRACYCLINS

=> carboplatin
L13      11377 CARBOPLATIN

=> cisplatin
L14      48403 CISPLATIN

=> taxol
L15      13986 TAXOL

=> taxotere
L16       1779 TAXOTERE

=> tamoxifen
L17      23697 TAMOXIFEN

=> estrogens
L18      68788 ESTROGENS
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=> interferons
L19     ' 79725 INTERFERONS

=> L3 and l4
L20           1 L3 AND L4

=> L3 and L5
L21           0 L3 AND L5

=> L3 and L6
L22           0 L3 AND L6

=> L3 and l7
L23           0 L3 AND L7

=> L3 and L9
L24           0 L3 AND L9

=> L3 and L10
L25           0 L3 AND L10

=> L3 and L11
L26           0 L3 AND L11

=> L3 and L12
L27           0 L3 AND L12

=> L23 and l14
L28           0 L23 AND L14

=> L3 and L15
L29           0 L3 AND L15

=> L3 and L16
L30           0 L3 AND L16

=> L3 and L17
L31           0 L3 AND L17

=> L3 and L18
L32           0 L3 AND L18

=> L19 and L3
L33           5 L19 AND L3

=> D L20 IBIB ABS

L20  ANSWER 1 OF 1  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
ACCESSION NUMBER:   2004:456513  BIOSIS
DOCUMENT NUMBER:    PREV200400454409
TITLE:              Oncolytic viruses for the treatment of cancer:
                    current strategies and clinical trials.
AUTHOR(S):          Ries, Stefan J. [Reprint Author]; Brandts, Christian H.
CORPORATE SOURCE:   MediGene AG, Lochhamer Str 11, D-82152, Martinsried,
                    Germany
                    cbrandts@uni-muenster.de
SOURCE:             Drug Discovery Today, (September 1 2004) Vol. 9, No. 17,
                    pp. 759-768. print.
                    ISSN: 1359-6446 (ISSN print).
DOCUMENT TYPE:      Article
                    General Review; (Literature Review)
LANGUAGE:           English
ENTRY DATE:         Entered STN: 24 Nov 2004
                    Last Updated on STN: 24 Nov 2004
AB   Tumor-selective replicating viruses offer appealing advantages over
     conventional cancer therapy and are a promising new approach for the
     treatment of human cancer.  The development of virotherapeutics is based
     on several strategies that each provides a different foundation for
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tumor-selective targeting and replication. Results emerging from clinical trials with **oncolytic** viruses demonstrate the safety and feasibility of a virotherapeutic approach and provide early indications of efficacy. Strategies to overcome potential obstacles and challenges to virotherapy are currently being explored and are discussed here. Importantly, the successful development of systemic administration of **oncolytic** viruses will extend the range of tumors that can be treated using this novel treatment modality.

=> D L33 IBIB ABS 1-5

L33 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1241018 CAPLUS
DOCUMENT NUMBER: 143:472560
TITLE: Mutated **oncolytic reoviruses** exhibiting hypersensitivity to interferon and improved ability to discriminate between normal and Ras-transformed cells, and anticancer uses
INVENTOR(S): Lemay, Guy; Danis, Carole; Rudd, Penny; Barkati, Sapha
PATENT ASSIGNEE(S): Universite De Montreal, Can.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005111200	A1	20051124	WO 2005-CA749	20050516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-571499P P 20040517
US 2004-574572P P 20040527

AB The present invention relates to a **reovirus** strain that is hypersensitive to interferon and more dependent on the transformed status of the host cells for its replication. Particularly, the present invention concerns isolates of mammalian **reovirus** MRV-3 (genus Orthoreovirus, serotype 3 Dearing) strains obtained by chemical mutagenesis and cloning. Provided is a **reovirus** MRV-3 strain P4L-12 exhibiting hypersensitivity to interferon and improved ability to discriminate between normal and Ras-transformed cells which comprises amino acids substitutions in σ3 and μ1 outer capsid proteins encoded resp. by S4 and M2 genes. This **reovirus** represents a promising alternative to wild type **reoviruses** for application as **oncolytic** agents in a clin. setting.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:494177 CAPLUS
DOCUMENT NUMBER: 143:209629
TITLE: Induction of p53-dependent apoptosis in HCT116 tumor cells by RNA viruses and possible implications in virus-mediated **oncolysis**
AUTHOR(S): Huang, Shirley; Qu, Li-Ke; Koromilas, Antonis E.
CORPORATE SOURCE: Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, QC,

Can.
SOURCE: Cell Cycle (2004), 3(8), 1043-1045
CODEN: CCEYAS; ISSN: 1538-4101
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent findings showed that type I **interferons** (IFNα/β) induce the transcription of tumor suppressor p53 and sensitize primary mouse embryonic fibroblasts (MEFs) to p53-mediated apoptosis by **oncolytic** viruses. However, the ability of RNA viruses to induce a p53-mediated apoptotic response may differ between primary and tumor cells and may be dependent upon the virus type. We have investigated this hypothesis by analyzing the apoptotic effects of various **oncolytic** viruses on the human colon carcinoma HCT116 cells and their derivs. lacking either p53 or bax gene. We show that HCT116 cells are resistant to the apoptotic effects of vesicular stomatitis virus, **reovirus** or poliovirus but activate the p53/Bax apoptotic pathway after infection with Sendai virus. These data substantiate the role of p53 in virus-mediated apoptosis and show that, unlike primary cells, tumor cells may be more selective in the activation of p53 pathway in response to the infection with specific types of viruses.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:615593 CAPLUS
DOCUMENT NUMBER: 142:32319
TITLE: Genetically targeted cancer therapy: Tumor destruction by PKR activation
AUTHOR(S): Vorburger, Stephan A.; Pataer, Abujiang; Swisher, Stephen G.; Hunt, Kelly K.
CORPORATE SOURCE: Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: American Journal of PharmacoGenomics (2004), 4(3), 189-198
CODEN: AJPMC8; ISSN: 1175-2203
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The double-stranded RNA-activated protein kinase (PKR) has been largely investigated for its key role in viral host defense. Although best characterized by its function in mediating the antiviral and antiproliferative effects of interferon (IFN), PKR is also implicated in transcriptional regulation, cell differentiation, signal transduction, and tumor suppression. However, recent findings identifying PKR as an important effector of apoptosis have led to an increased interest in PKR modulation as an antitumor strategy. PKR can either be up-regulated through direct induction by the transcription factor E2F-1, or it can be activated through direct protein-protein interactions with the melanoma differentiation-associated gene-7 (MDA7, IL-24). Addnl., the intracellular formation of double-stranded RNA by transfection with antisense RNA complementary to tumor-specific RNA sequences can induce PKR activation and apoptosis selective to these tumor cells. The growing application of viral vector-based gene therapies and **oncolytic**, replicating viruses that must elude viral defense in order to be effective, has also drawn attention to PKR. **Oncolytic** viruses, like the attenuated herpes simplex virus R3616, the vesicular stomatitis virus, or **reovirus**, specifically replicate in tumor cells only because the viral host defense in the permissive cells is suppressed. In this article we review the role of PKR as an effector of apoptosis and a target for tumor treatment strategies and discuss the potential of PKR-modifying agents to treat patients with cancer. Targeted gene therapy against cancer can be approached by activation of PKR with the down-regulation of protein synthesis and induction of apoptosis, or by suppression of PKR with the propagation of **oncolytic** virus. Since the PKR pathway can be modified by many routes, antitumor therapies combining **oncolytic** virus, gene therapies, and chemotherapy with PKR modifiers are likely to emerge in the near future as therapeutic options in the treatment of patients with cancer.

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:318006 CAPLUS
DOCUMENT NUMBER: 141:33169
TITLE: Tumor-targeting gene therapy: ras-dependent **oncolytic** viral vectors
AUTHOR(S): Hamada, Hirofumi
CORPORATE SOURCE: Dep. of Molecular Medicine, Sapporo Medical University, Sapporo, 060-8556, Japan
SOURCE: Uirusu (2003), 53(2), 195-199
CODEN: UIRUAF; ISSN: 0042-6857
PUBLISHER: Nippon Uirusu Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Tumor-targeting gene therapy with ras-dependent **oncolytic** viral vectors is reviewed including the Ras and interferon signal pathway, ras-dependent **reovirus**, Ras selective influenza virus and herpes simplex virus, ras-dependent **oncolysis** with an adenovirus VA I mutant in cancer therapy, and clin. application with examples.

L33 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:20988 CAPLUS
DOCUMENT NUMBER: 140:73576
TITLE: **Oncolytic** viruses as phenotyping agents for neoplasms and use for tumor diagnosis and therapy
INVENTOR(S): Thompson, Bradley G.; Coffey, Matthew C.
PATENT ASSIGNEE(S): Oncolytics Biotech, Inc., Can.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004003562	A2	20040108	WO 2003-CA951		20030625
WO 2004003562	A3	20040506			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004029112	A1	20040212	US 2003-602024		20030624
CA 2487824	AA	20040108	CA 2003-2487824		20030625
AU 2003245760	A1	20040119	AU 2003-245760		20030625
EP 1520175	A2	20050406	EP 2003-737795		20030625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003011983	A	20050426	BR 2003-11983		20030625
CN 1666105	A	20050907	CN 2003-815353		20030625
JP 2005531306	T2	20051020	JP 2004-516379		20030625
PRIORITY APPLN. INFO.:			US 2002-392031P	P	20020628
			US 2003-443188P	P	20030129
			WO 2003-CA951	W	20030625

AB The present invention provides a method of diagnosing neoplasms having a particular phenotype by using **oncolytic** viruses that selectively replicate in neoplasms having the particular phenotype. For example, **reovirus** does not replicate in normal cells. However, **reovirus** selectively replicate in cells with an activated ras

pathway, which leads to death of these cells. Therefore, a cell which becomes neoplastic due to, at least in part, elevated ras pathway activities can be diagnosed by its susceptibility to **reovirus** replication. This invention can further be applied, using other **oncolytic** viruses, to the diagnosis and/or treatment of other tumors, such as interferon-sensitive tumors, p53-deficient tumors and Rb-deficient tumors. Kits useful in the diagnosis or treatment disclosed herein are also provided.

=> chemotherapy
L34 177973 CHEMOTHERAPY

=> L3 and L34
L35 6 L3 AND L34

=> D L35 IBIB ABS 1-6

L35 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:186404 CAPLUS
DOCUMENT NUMBER: 144:323988
TITLE: **Oncolytic** viruses for the treatment of malignant glioma
AUTHOR(S): Merrill, Melinda K.; Selznick, Lee A.; Gromeier, Matthias
CORPORATE SOURCE: Department of Molecular Genetics & Microbiology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Expert Opinion on Therapeutic Patents (2006), 16(3), 363-371
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Malignant glioma is the most common primary malignancy of the human CNS. Despite decades of research, the current therapeutic strategy consists of a multimodal regimen of surgery, **chemotherapy**, and radiation. This course of therapy yields a median survival after diagnosis of .apprx.1 yr. This dismal prognosis inspires the ongoing development of novel **oncolytic** agents targeting glioma, which include gene therapy, immunomodulatory therapy, and **oncolytic** viruses. **Oncolytic** viruses are defined by their ability to target, replicate in, and lyse tumor cells without critically damaging surrounding noncancerous tissue. Although some viruses are naturally **oncolytic** and tumor-selective, the advent of modern recombinant DNA technol. has allowed the engineering of addnl. viruses with improved therapeutic indexes. This technol. advance has enabled rapid growth in the field of viral therapy. **Reovirus**, Newcastle disease virus (NDV), measles virus, adenovirus, poliovirus, and herpes simplex virus 1 are in preclin. and clin. development for use as **oncolytic** agents against malignant glioma. This report focuses on the recent patent literature in the field of **oncolytic** viruses for the treatment of malignant glioma.
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:29223 CAPLUS
DOCUMENT NUMBER: 142:107380
TITLE: **Oncolytic** viruses for the treatment of neoplasms having activated protein phosphatase 2A (PP2A) or Rac
INVENTOR(S): Lee, Patrick W. K.; Norman, Kara L.
PATENT ASSIGNEE(S): Oncolytics Biotech Inc., Can.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002607	A2	20050113	WO 2004-CA986	20040706
WO 2005002607	A3	20050506		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2434995	AA	20050107	CA 2003-2434995	20030707
US 2005019308	A1	20050127	US 2004-886022	20040706
PRIORITY APPLN. INFO.:			US 2003-484643P P	20030707

AB Methods are disclosed for treating neoplasms by administering **oncolytic** viruses to a neoplasm having activated PP2A-like or Rac activities. The virus is administered so that it ultimately directly contacts target cancer cells. Combinations of more than one type and/or strain of **oncolytic** viruses can be used. Of particular interest is the use of **reovirus**.

L35 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:615593 CAPLUS
DOCUMENT NUMBER:	142:32319
TITLE:	Genetically targeted cancer therapy: Tumor destruction by PKR activation
AUTHOR(S):	Vorburger, Stephan A.; Pataer, Abujiang; Swisher, Stephen G.; Hunt, Kelly K.
CORPORATE SOURCE:	Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE:	American Journal of PharmacoGenomics (2004), 4(3), 189-198 CODEN: AJPMC8; ISSN: 1175-2203
PUBLISHER:	Adis International Ltd.
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. The double-stranded RNA-activated protein kinase (PKR) has been largely investigated for its key role in viral host defense. Although best characterized by its function in mediating the antiviral and antiproliferative effects of interferon (IFN), PKR is also implicated in transcriptional regulation, cell differentiation, signal transduction, and tumor suppression. However, recent findings identifying PKR as an important effector of apoptosis have led to an increased interest in PKR modulation as an antitumor strategy. PKR can either be up-regulated through direct induction by the transcription factor E2F-1, or it can be activated through direct protein-protein interactions with the melanoma differentiation-associated gene-7 (MDA7, IL-24). Addnl., the intracellular formation of double-stranded RNA by transfection with antisense RNA complementary to tumor-specific RNA sequences can induce PKR activation and apoptosis selective to these tumor cells. The growing application of viral vector-based gene therapies and **oncolytic**, replicating viruses that must elude viral defense in order to be effective, has also drawn attention to PKR. **Oncolytic** viruses, like the attenuated herpes simplex virus R3616, the vesicular stomatitis virus, or **reovirus**, specifically replicate in tumor cells only because the viral host defense in the permissive cells is suppressed. In this article we review the role of PKR as an effector of apoptosis and a target for tumor treatment strategies and discuss the potential of PKR-modifying agents to treat patients with cancer. Targeted gene therapy against cancer can be approached by activation of PKR with the down-regulation of protein synthesis and induction of apoptosis, or by suppression of PKR with the propagation of **oncolytic** virus. Since the PKR pathway can be modified by many routes, antitumor therapies combining **oncolytic** virus, gene therapies, and **chemotherapy** with

PKR modifiers are likely to emerge in the near future as therapeutic options in the treatment of patients with cancer.

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:913020 CAPLUS
DOCUMENT NUMBER: 139:375000
TITLE: Method for reducing pain using **oncolytic** viruses
INVENTOR(S): Morris, Donald; Coffey, Matthew C.; Thompson, Bradley G.
PATENT ASSIGNEE(S): Oncolytics Biotech Inc., Can.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003094938	A1	20031120	WO 2003-CA674	20030507
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003229431	A1	20031111	AU 2003-229431	20030507
CA 2484398	AA	20031120	CA 2003-2484398	20030507
EP 1505992	A1	20050216	EP 2003-722131	20030507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003009825	A	20050301	BR 2003-9825	20030507
TR 200501460	T3	20050621	TR 2005-200501460	20030507
JP 2005526124	T2	20050902	JP 2004-503021	20030507
US 2004091458	A1	20040513	US 2003-431580	20030508
PRIORITY APPLN. INFO.:			US 2002-378675P P	20020509
			US 2003-443177P P	20030129
			WO 2003-CA674 W	20030507

AB The invention provides a method for reducing pain associated with neoplasms in a mammal, comprising administering an effective amount of one or more **oncolytic** viruses. Preferably, the mammal also receives an analgesic, and the amount of analgesic required by the mammal is reduced when the **oncolytic** virus is administered. The **oncolytic** virus is preferably **reovirus**. The mammal may be addnl. subject to **chemotherapy**, immunotherapy, hormonal and/or radiation therapy. For example, a patient suffering from malignant melanoma and being permanently on narcotics received three intratumoral injections of 109 pfu of the Dearing strain of **reovirus** serotype 3. One week following injection, the patient reported diminished pain at the treatment site and was taken off narcotics. There was no pain at the treatment site during a 8-10 wk period after injection and no significant side effects.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:52085 CAPLUS
DOCUMENT NUMBER: 132:193045
TITLE: **Oncolytic** viruses as novel anticancer agents: turning one scourge against another
AUTHOR(S): Smith, Edward R.; Chiocca, E. Antonio
CORPORATE SOURCE: Molecular Neuro-oncology Laboratories, Neurosurgery

Service, Massachusetts General Hospital, CNY6, Charlestown, MA, 02119, USA
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(2), 311-327
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 140 refs. Although the use of viruses as **oncolytic** agents is an historic concept, the use of genetically modified viruses to selectively target tumor cells is relatively novel and recent. The ability of viruses to efficiently infect and lyse cells, combined with the potential augmentation of this effect by progeny viruses throughout the tumor provide justification for exploitation of these agents in cancer therapy. Before application to humans, though, issues related to tumor cell selectivity, lack of toxicity to normal tissues and the effect of the antiviral immune response, will have to be clarified. The more commonly used **oncolytic** viruses are based on mutant strains of herpes simplex virus, adenovirus and **reovirus**. The tumor selectivity of each of these strains is discussed, particularly the complementation of the viral defect by cellular pathways involved in tumorigenesis. The combination of **oncolytic** viruses with radiation, **chemotherapy** and gene therapy is also reviewed. Further study of the interaction of viral proteins with cellular pathways involved in cell cycle control will provide the rationale for viral mutants with increased selectivity for tumor cells.

REFERENCE COUNT: 140 THERE ARE 140 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 6 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:189830 BIOSIS
DOCUMENT NUMBER: PREV200500189862
TITLE: **Oncolytic** viruses for cancer therapy I. Cell-external factors: Virus entry and receptor interaction.
AUTHOR(S): Campbell, Stephanie A.; Gromeier, Matthias [Reprint Author]
CORPORATE SOURCE: Med CtrDept Mol Genet and Microbiol, Duke Univ, Box 3020, Durham, NC, 27710, USA
grome001@mc.duke.edu
SOURCE: Onkologie, (2005) Vol. 28, No. 3, pp. 144-149. print.
CODEN: ONKOD2. ISSN: 0378-584X.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 2005
Last Updated on STN: 18 May 2005

AB After being recognized for their anti-neoplastic properties at the beginning of the last century, viruses are again being considered for use as therapeutic agents against cancer. Certain virus species have a propensity to replicate within transformed cells, which are commonly rendered vulnerable due to tumor-specific defects in their defense against viral infection. Other viruses have been modified to subject them to tumor-specific growth conditions. **Oncolytic** viruses carry the promise to efficiently target cancer cells for destruction and spread throughout tumor tissue to reach distant neoplastic loci without causing collateral damage to healthy tissues. In contrast to conventional cancer **chemotherapy**, viral anti-neoplastic agents require complex interactions with the host organism to reach their target and to unfold their **oncolytic** activity. Recent progress in the elucidation of the molecular mechanisms of viral pathogenesis has opened up new opportunities to manipulate virus-host interactions, generating effective anti-tumor strategies. On the other hand, significant obstacles towards the application of safe and efficacious viral therapies have become apparent. These frequently relate to the lack of cell culture and animal tumor models that accurately reflect the characteristics of cancerous tissues in patients. Throughout the past century, viral therapeutics against cancer have evolved into a new class of treatment strategies characterized by unique opportunities and challenges. A growing number of

oncolytic viruses has entered clinical investigation or is scheduled to do so in the near future. Great efforts are being undertaken to rekindle an old idea and, with the help of new technologies, to realize its promise of new treatment facilities for cancer.

=> L1 and L34
L36 204 L1 AND L34

=> interferon and l1
L37 116 INTERFERON AND L1

=> reovirus and l37
L38 9 REOVIRUS AND L37

=> D L38 IBIB ABS 1-9

L38 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1241018 CAPLUS
DOCUMENT NUMBER: 143:472560
TITLE: Mutated **oncolytic reoviruses** exhibiting hypersensitivity to **interferon** and improved ability to discriminate between normal and Ras-transformed cells, and anticancer uses
INVENTOR(S): Lemay, Guy; Danis, Carole; Rudd, Penny; Barkati, Sapha
PATENT ASSIGNEE(S): Universite De Montreal, Can.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005111200	A1	20051124	WO 2005-CA749	20050516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-571499P P 20040517
US 2004-574572P P 20040527

AB The present invention relates to a **reovirus** strain that is hypersensitive to **interferon** and more dependent on the transformed status of the host cells for its replication. Particularly, the present invention concerns isolates of mammalian **reovirus** MRV-3 (genus Orthoreovirus, serotype 3 Dearing) strains obtained by chemical mutagenesis and cloning. Provided is a **reovirus** MRV-3 strain P4L-12 exhibiting hypersensitivity to **interferon** and improved ability to discriminate between normal and Ras-transformed cells which comprises amino acids substitutions in σ3 and μ1 outer capsid proteins encoded resp. by S4 and M2 genes. This **reovirus** represents a promising alternative to wild type **reoviruses** for application as **oncolytic** agents in a clin. setting.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1038075 CAPLUS
DOCUMENT NUMBER: 144:120509
TITLE: Influenza A viruses with deletions in the NS1 gene- a

rational approach to develop **oncolytic** viruses
AUTHOR(S): Bergmann, Michael; Muster, Thomas
CORPORATE SOURCE: Department of Surgery, University of Vienna Medical School, Vienna, Austria
SOURCE: Viral Therapy of Human Cancers (2005), 575-596. Editor(s): Sinkovics, Joseph G.; Horvath, Joseph C. Marcel Dekker, Inc.: New York, N. Y. CODEN: 69HIM6; ISBN: 0-8247-5913-3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review discusses the principle and characterization of influenza A virus mediated **oncolysis**. Topics discussed include characteristics of the genome; introduction of mutations into the genome of influenza virus; the DELNS1 virus; the **interferon** pathway and the NS1 protein; tumor-associated defects of the **interferon** pathway; influenza A virus mediated **oncolysis** in **interferon** resistant tumors; influenza A virus-mediated **oncolysis** in tumor expression of oncogenic RAS; properties of influenza A virus for virotherapy; and **oncolytic reoviruses**.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:494177 CAPLUS
DOCUMENT NUMBER: 143:209629
TITLE: Induction of p53-dependent apoptosis in HCT116 tumor cells by RNA viruses and possible implications in virus-mediated **oncolysis**
AUTHOR(S): Huang, Shirley; Qu, Li-Ke; Koromilas, Antonis E.
CORPORATE SOURCE: Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, QC, Can.
SOURCE: Cell Cycle (2004), 3(8), 1043-1045 CODEN: CCEYAS; ISSN: 1538-4101
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent findings showed that type I **interferons** (IFNα/β) induce the transcription of tumor suppressor p53 and sensitize primary mouse embryonic fibroblasts (MEFs) to p53-mediated apoptosis by **oncolytic** viruses. However, the ability of RNA viruses to induce a p53-mediated apoptotic response may differ between primary and tumor cells and may be dependent upon the virus type. We have investigated this hypothesis by analyzing the apoptotic effects of various **oncolytic** viruses on the human colon carcinoma HCT116 cells and their derivs. lacking either p53 or bax gene. We show that HCT116 cells are resistant to the apoptotic effects of vesicular stomatitis virus, **reovirus** or poliovirus but activate the p53/Bax apoptotic pathway after infection with Sendai virus. These data substantiate the role of p53 in virus-mediated apoptosis and show that, unlike primary cells, tumor cells may be more selective in the activation of p53 pathway in response to the infection with specific types of viruses.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:615593 CAPLUS
DOCUMENT NUMBER: 142:32319
TITLE: Genetically targeted cancer therapy: Tumor destruction by PKR activation
AUTHOR(S): Vorburger, Stephan A.; Pataer, Abujiang; Swisher, Stephen G.; Hunt, Kelly K.
CORPORATE SOURCE: Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: American Journal of PharmacoGenomics (2004), 4(3), 189-198 CODEN: AJPMC8; ISSN: 1175-2203
PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The double-stranded RNA-activated protein kinase (PKR) has been largely investigated for its key role in viral host defense. Although best characterized by its function in mediating the antiviral and antiproliferative effects of **interferon** (IFN), PKR is also implicated in transcriptional regulation, cell differentiation, signal transduction, and tumor suppression. However, recent findings identifying PKR as an important effector of apoptosis have led to an increased interest in PKR modulation as an antitumor strategy. PKR can either be up-regulated through direct induction by the transcription factor E2F-1, or it can be activated through direct protein-protein interactions with the melanoma differentiation-associated gene-7 (MDA7, IL-24). Addnl., the intracellular formation of double-stranded RNA by transfection with antisense RNA complementary to tumor-specific RNA sequences can induce PKR activation and apoptosis selective to these tumor cells. The growing application of viral vector-based gene therapies and **oncolytic**, replicating viruses that must elude viral defense in order to be effective, has also drawn attention to PKR. **Oncolytic** viruses, like the attenuated herpes simplex virus R3616, the vesicular stomatitis virus, or **reovirus**, specifically replicate in tumor cells only because the viral host defense in the permissive cells is suppressed. In this article we review the role of PKR as an effector of apoptosis and a target for tumor treatment strategies and discuss the potential of PKR-modifying agents to treat patients with cancer. Targeted gene therapy against cancer can be approached by activation of PKR with the down-regulation of protein synthesis and induction of apoptosis, or by suppression of PKR with the propagation of **oncolytic** virus. Since the PKR pathway can be modified by many routes, antitumor therapies combining **oncolytic** virus, gene therapies, and chemotherapy with PKR modifiers are likely to emerge in the near future as therapeutic options in the treatment of patients with cancer.
REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:318006 CAPLUS
DOCUMENT NUMBER: 141:33169
TITLE: Tumor-targeting gene therapy: ras-dependent **oncolytic** viral vectors
AUTHOR(S): Hamada, Hirofumi
CORPORATE SOURCE: Dep. of Molecular Medicine, Sapporo Medical University, Sapporo, 060-8556, Japan
SOURCE: Uirusu (2003), 53(2), 195-199
CODEN: UIRUAF; ISSN: 0042-6857
PUBLISHER: Nippon Uirusu Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Tumor-targeting gene therapy with ras-dependent **oncolytic** viral vectors is reviewed including the Ras and **interferon** signal pathway, ras-dependent **reovirus**, Ras selective influenza virus and herpes simplex virus, ras-dependent **oncolysis** with an adenovirus VA I mutant in cancer therapy, and clin. application with examples.

L38 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:20988 CAPLUS
DOCUMENT NUMBER: 140:73576
TITLE: **Oncolytic** viruses as phenotyping agents for neoplasms and use for tumor diagnosis and therapy
INVENTOR(S): Thompson, Bradley G.; Coffey, Matthew C.
PATENT ASSIGNEE(S): Oncolytics Biotech, Inc., Can.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004003562	A2	20040108	WO 2003-CA951		20030625
WO 2004003562	A3	20040506			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004029112	A1	20040212	US 2003-602024		20030624
CA 2487824	AA	20040108	CA 2003-2487824		20030625
AU 2003245760	A1	20040119	AU 2003-245760		20030625
EP 1520175	A2	20050406	EP 2003-737795		20030625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003011983	A	20050426	BR 2003-11983		20030625
CN 1666105	A	20050907	CN 2003-815353		20030625
JP 2005531306	T2	20051020	JP 2004-516379		20030625
PRIORITY APPLN. INFO.:			US 2002-392031P	P	20020628
			US 2003-443188P	P	20030129
			WO 2003-CA951	W	20030625

AB The present invention provides a method of diagnosing neoplasms having a particular phenotype by using **oncolytic** viruses that selectively replicate in neoplasms having the particular phenotype. For example, **reovirus** does not replicate in normal cells. However, **reovirus** selectively replicate in cells with an activated ras pathway, which leads to death of these cells. Therefore, a cell which becomes neoplastic due to, at least in part, elevated ras pathway activities can be diagnosed by its susceptibility to **reovirus** replication. This invention can further be applied, using other **oncolytic** viruses, to the diagnosis and/or treatment of other tumors, such as **interferon**-sensitive tumors, p53-deficient tumors and Rb-deficient tumors. Kits useful in the diagnosis or treatment disclosed herein are also provided.

L38 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2003:16711 CAPLUS
DOCUMENT NUMBER:	139:139
TITLE:	RNA viruses as virotherapy agents
AUTHOR(S):	Russell, Stephen J.
CORPORATE SOURCE:	Mayo Clinic, Molecular Medicine Program, Rochester, MN, 55905, USA
SOURCE:	Cancer Gene Therapy (2002), 9(12), 961-966 CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER:	Nature Publishing Group
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. RNA viruses are rapidly emerging as extraordinarily promising agents for **oncolytic** virotherapy. Integral to the lifecycles of all RNA viruses is the formation of double-stranded RNA, which activates a spectrum of cellular defense mechanisms including the activation of PKR and the release of **interferon**. Tumors are frequently defective in their PKR signaling and **interferon** response pathways, and therefore provide a relatively permissive substrate for the propagation of RNA viruses. For most of the **oncolytic** RNA viruses currently under study, tumor specificity is either a natural characteristic of the virus, or a serendipitous consequence of adapting the virus to propagate in human tumor cell lines. Further refinement and optimization of these **oncolytic** agents can be achieved through virus engineering. This article provides a summary of the current status of **oncolytic** virotherapy efforts for seven different RNA viruses, namely, mumps, Newcastle disease virus, measles virus, vesicular stomatitis virus, influenza, **reovirus**, and poliovirus.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:456513 BIOSIS
DOCUMENT NUMBER: PREV200400454409
TITLE: **Oncolytic** viruses for the treatment of cancer: current strategies and clinical trials.
AUTHOR(S): Ries, Stefan J. [Reprint Author]; Brandts, Christian H.
CORPORATE SOURCE: MediGene AG, Lochhamer Str 11, D-82152, Martinsried, Germany
cbrandts@uni-muenster.de
SOURCE: Drug Discovery Today, (September 1 2004) Vol. 9, No. 17, pp. 759-768. print.
ISSN: 1359-6446 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Nov 2004
Last Updated on STN: 24 Nov 2004

AB Tumor-selective replicating viruses offer appealing advantages over conventional cancer therapy and are a promising new approach for the treatment of human cancer. The development of virotherapeutics is based on several strategies that each provides a different foundation for tumor-selective targeting and replication. Results emerging from clinical trials with **oncolytic** viruses demonstrate the safety and feasibility of a virotherapeutic approach and provide early indications of efficacy. Strategies to overcome potential obstacles and challenges to virotherapy are currently being explored and are discussed here. Importantly, the successful development of systemic administration of **oncolytic** viruses will extend the range of tumors that can be treated using this novel treatment modality.

L38 ANSWER 9 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:70348 BIOSIS
DOCUMENT NUMBER: PREV200300070348
TITLE: RNA viruses as virotherapy agents.
AUTHOR(S): Russell, Stephen J. [Reprint Author]
CORPORATE SOURCE: Molecular Medicine Program, Mayo Clinic, 200 First Street, SW, Rochester, MN, 55905, USA
sjr@mayo.edu
SOURCE: Cancer Gene Therapy, (December 2002) Vol. 9, No. 12, pp. 961-966. print.
ISSN: 0929-1903 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jan 2003
Last Updated on STN: 29 Jan 2003

AB RNA viruses are rapidly emerging as extraordinarily promising agents for **oncolytic** virotherapy. Integral to the lifecycles of all RNA viruses is the formation of double-stranded RNA, which activates a spectrum of cellular defense mechanisms including the activation of PKR and the release of **interferon**. Tumors are frequently defective in their PKR signaling and **interferon** response pathways, and therefore provide a relatively permissive substrate for the propagation of RNA viruses. For most of the **oncolytic** RNA viruses currently under study, tumor specificity is either a natural characteristic of the virus, or a serendipitous consequence of adapting the virus to propagate in human tumor cell lines. Further refinement and optimization of these **oncolytic** agents can be achieved through virus engineering. This article provides a summary of the current status of **oncolytic** virotherapy efforts for seven different RNA viruses, namely, mumps, Newcastle disease virus, measles virus, vesicular stomatitis virus, influenza, **reovirus**, and poliovirus.

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L38 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1241018 CAPLUS
DOCUMENT NUMBER: 143:472560
TITLE: Mutated **oncolytic reoviruses**
exhibiting hypersensitivity to **interferon**
and improved ability to discriminate between normal
and Ras-transformed cells, and anticancer uses
INVENTOR(S): Lemay, Guy; Danis, Carole; Rudd, Penny; Barkati, Sapha
PATENT ASSIGNEE(S): Universite De Montreal, Can.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005111200	A1	20051124	WO 2005-CA749	20050516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
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NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-571499P P 20040517
US 2004-574572P P 20040527
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D history

(FILE 'HOME' ENTERED AT 11:02:03 ON 25 APR 2006)

FILE 'CAPLUS, BIOSIS' ENTERED AT 11:02:15 ON 25 APR 2006
L1 2263 ONCOLYTIC OR ONCOLYSIS
L2 5743 REOVIRUS
L3 95 L1 AND L2
L4 43156 FLUOROURACIL
L5 27736 MITOMYCIN
L6 37 METHOTHREXATE
L7 3 HYDROXYRUEA
L8 0 CYCLOPHOSPHASMID
L9 57023 CYCLOPHOSPHAMIDE
L10 3183 DACARBAZINE
L11 7894 MITOXANTRONE
L12 95 ANTHRACYCLINS
L13 11377 CARBOPLATIN
L14 48403 CISPLATIN

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L15        13986 TAXOL
L16         1779 TAXOTERE
L17        23697 TAMOXIFEN
L18        68788 ESTROGENS
L19        79725 INTERFERONS
L20            1 L3 AND L4
L21            0 L3 AND L5
L22            0 L3 AND L6
L23            0 L3 AND L7
L24            0 L3 AND L9
L25            0 L3 AND L10
L26            0 L3 AND L11
L27            0 L3 AND L12
L28            0 L23 AND L14
L29            0 L3 AND L15
L30            0 L3 AND L16
L31            0 L3 AND L17
L32            0 L3 AND L18
L33            5 L19 AND L3
L34       177973 CHEMOTHERAPY
L35            6 L3 AND L34
L36          204 L1 AND L34
L37          116 INTERFERON AND L1
L38            9 REOVIRUS AND L37

=> L14 and L1
L39           47 L14 AND L1

=> reovirus
L40         5743 REOVIRUS

=> L40 and l39
L41            0 L40 AND L39

=> L15 and l1
L42           14 L15 AND L1

=> reovirus
L43         5743 REOVIRUS

=> L43 and l42
L44            0 L43 AND L42

=> l9 and l1
L45           67 L9 AND L1

=> L45 and l2
L46            0 L45 AND L2

=> D l42 IBIB ABS 1-14

L42  ANSWER 1 OF 14  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:763184  CAPLUS
DOCUMENT NUMBER:          140:210048
TITLE:                    Oncolytic viral therapy for human ovarian
                          cancer using a novel replication-competent herpes
                          simplex virus type I mutant in a mouse model
AUTHOR(S):                Nawa, Akihiro; Nozawa, Naoki; Goshima, Fumi; Nagasaka,
                          Tetsuo; Kikkawa, Fumitaka; Niwa, Yoshimitsu;
                          Nakanishi, Toru; Kuzuya, Kazuo; Nishiyama, Yukihiro
CORPORATE SOURCE:         Department of Gynecology, Aichi Cancer Center
                          Hospital, Chikusa-ku, Nagoya, 464-8681, Japan
SOURCE:                   Gynecologic Oncology (2003), 91(1), 81-88
                          CODEN: GYNOA3; ISSN: 0090-8258
PUBLISHER:                Elsevier Science
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Objectives: Attenuated mutant strains of herpes simplex virus (HSV) have
     been effectively used for treatment of malignant brain tumors.  As HSV-1
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can infect and lyse a variety of cell types, other malignancies may also benefit from such treatment. We sought to test the feasibility of HSV-1 mutant-mediated gene therapy treatment of ovarian cancer. Methods: We prepared two attenuated mutant HSV-1 strains. An HSV-1 mutant, hrR3, has replaced the gene encoding ribonucleotide reductase (RR) with the lacZ reporter gene. We also developed a new replication-competent HSV-1 mutant, HR522; this virus, expressing the lacZ reporter gene, induces syncytium formation in infected cells. We compared the efficacy of HR522 with, paclitaxel (**Taxol**) and hrR3 in the treatment of nude mice harboring human ovarian cancer cells. We also examined the effect of the prodrug ganciclovir (GCV) on the treatment mediated by these HSVs. Survival was evaluated by Kaplan-Meier method and log-rank test. Results: The survival of mice treated with a high-titer hrR3 (5 + 107 plaque-forming units [PFU]) was significantly prolonged as compared with the group given paclitaxel. Although the survival of mice treated with high-titer HR522 (5 + 107 PFU) was not significantly prolonged compared with paclitaxel-treated group, GCV markedly enhanced the efficacy of HR522 administration. The lacZ gene product, visualized using 5-bromo-4-chloro-3-indolyl-β-d-galactopyranoside (X-gal) histochem., was detected in HR522-treated tumors in areas also exhibiting apoptotic changes. Conclusions: These findings indicate that the combination of HR522 and GCV possesses significant therapeutic potential for treatment of ovarian cancer. Such viral therapy offers a novel approach to redns. in the dissemination of ovarian cancer.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:675779 CAPLUS
DOCUMENT NUMBER: 137:210924
TITLE: **Oncolytic** adenoviral vectors expressing therapeutic genes for the treatment of cancer
INVENTOR(S): Ennist, David Leonard; Forry-Schaudies, Suzanne; Gorziglia, Mario; Hallenbeck, Paul L.; Hay, Carl M.; Jakubczak, John Leonard; Kaleko, Michael; Ryan, Patricia Clara; Stewart, David A.; Xie, Yuefeng; Connelly, Sheila; Police, Sehidhar Reddy; Clarke, Lori; Phipps, Sandrina; Cheng, Cheng
PATENT ASSIGNEE(S): Novartis Pharma AG, Switz.; Novartis AG
SOURCE: PCT Int. Appl., 226 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002067861	A2	20020906	WO 2002-US5300		20020222
WO 2002067861	A3	20030821			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2439115	AA	20020906	CA 2002-2439115		20020222
US 2003104625	A1	20030605	US 2002-81969		20020222
EP 1377671	A2	20040107	EP 2002-714960		20020222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004529627	T2	20040930	JP 2002-567233		20020222
PRIORITY APPLN. INFO.:			US 2001-270922P	P	20010223
			US 2001-295037P	P	20010601
			US 2002-348670P	P	20020114

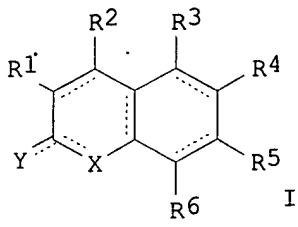
WO 2002-US5300 W 20020222

AB The present invention relates to **oncolytic** adenoviral vectors and their use in methods of gene therapy. Provided is a recombinant viral vector comprising an adenoviral nucleic acid backbone, wherein said nucleic acid backbone comprises in sequential order: a left ITR, a termination signal sequence, an E2F responsive promoter which is operably linked to a gene essential for replication of the recombinant viral vector, an adenoviral packaging signal, and a right ITR. The adenoviral vectors may also comprise a polynucleotide encoding a cytokine such as GM-CSF that can stimulate a systemic immune response against tumor cells. The preferred vector Ar6pAE2fF comprises an adenovirus vector that uses a fragment of the human E2F-1 promoter to selectively regulate E1A expression and thus adenoviral replication in tumor cells. Ar6pAE2fF selectively kills Rb-pathway defective tumor cells over normal primary cells, and is preferentially replicated in human tumor cell lines vs. normal primary cells. This vector has a superior early toxicity profile to the non-selective replication competent virus, Addl327, when administered i.v. in SCID mice and provides advantages in efficacy, selectivity, and safety as compared to the **oncolytic** viral vector Addl1520. Ar17pAE2fTrtex is a particularly preferred, tumor-selective **oncolytic** adenovirus designed for the treatment of a broad range of cancer indications involving the two most common alterations in human cancer, namely defects in the Rb-pathway and overexpression of telomerase. Ar17pAE2fTrtex utilizes a E2F-1 promoter to control expression of the adenoviral E1A gene and the adenoviral E4 gene is controlled by a hTERT (human telomerase reverse transcriptase) promoter. Ar17pAE2fTrtex is expected to replicate in the majority of cancer cells, lead to tumor selective expression of toxic viral proteins, cytolysis, and enhancement of sensitivity to chemotherapy, cytokines, and cytotoxic T lymphocytes.

L42 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:618006 CAPLUS
DOCUMENT NUMBER: 135:195449
TITLE: Coumarin derivatives as P-glycoprotein inhibitors for enhancing the antimicrobial and antitumor activities of other antimicrobial and cytotoxic agents
INVENTOR(S): Gumbleton, Mark; Abulrob, Abedel-nasser; Russell, Allan Denver; Simons, Claire
PATENT ASSIGNEE(S): University College Cardiff Consultants Limited, UK
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060827	A1	20010823	WO 2001-GB689	20010219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: GB 2000-3685 A 20000217
OTHER SOURCE(S): MARPAT 135:195449
GI



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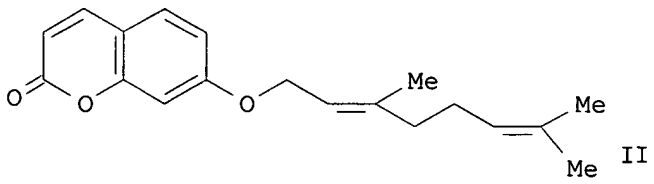


II

AB Coumarin derivs., such as I [X = CH, CH2, NH, O, S; Y = H, O; R1 = H, alkyl, NH2, aminoalkyl, OR5; R2-R4 = H, OH, alkoxy, OR5; R3R4 = 5 or 6 membered heterocyclic ring; R5 = C5-20 alkyl, C5-20 alkenyl, C5-20 alkylene(C3-6 cycloalkyl), C5-20 alkenylene(C3-6cycloalkyl), C5-20 alkylene(heterocycle) and C5-20 alkenylene(heterocycle), where heterocycle represents a 3 to 5 membered heterocyclic ring containing at least one oxygen heteroatom and where said cycloalkyl or heterocycle can be substituted with one or more C1-4 alkyl; dashed line = single bond or double bond], a pharmaceutically acceptable salt or prodrug thereof, were either isolated from grapefruit oil or prepared as P-glycoprotein inhibiting compds. for lowering the resistance of target cells to selected therapeutic agents. The coumarin derivs. were tested as P-glycoprotein inhibitors for enhancing the antimicrobial and antitumor activities of other antimicrobial and cytotoxic agents. Thus, coumarin derivative II isolated from grapefruit oil combined with ethidium bromide showed susceptibility (MIC) of methicillin sensitive staphylococcus aureus (MSSA) at a concentration of 30μg/mL. The P-glycoprotein inhibitory activity for II (20μg/mL) in MCF-7/ADR cells was compared with verapamil (40μg/mL).

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:65164 CAPLUS
DOCUMENT NUMBER: 128:152347
TITLE: Neuroprotection in diabetic and toxic neuropathies
AUTHOR(S): Hamers, Frank P. T.; Biessels, Geert Jan; Van Dam, P. Sytze; Gispen, Willem Hendrik
CORPORATE SOURCE: Rudolf Magnus Institute for Neurosciences, Utrecht, Neth.
SOURCE: Neuroprotection in CNS Diseases (1997), 513-554. Editor(s): Baer, P. R.; Beal, M. Flint. Dekker: New York, N. Y.
CODEN: 65OGAT
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review, with 359 refs., on diabetic neuropathy and neuropathies induced by the **oncolytics** cisplatin and **taxol**. Topics discussed include: correction of the microenvironment of the nerve in exptl. diabetic neuropathy, neurotrophic factors in diabetic neuropathy, cisplatin- and **taxol**-induced neuropathies, therapeutic options, free radical scavengers and(or) chelators in cisplatin neuropathy and neurotrophic factors in cisplatin/**taxol** neuropathy.

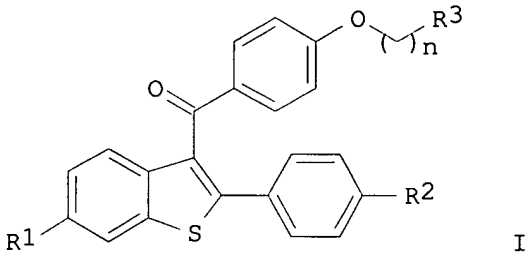
REFERENCE COUNT: 339 THERE ARE 339 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:433530 CAPLUS
DOCUMENT NUMBER: 127:50535
TITLE: Benzothiophene derivatives for treating resistant tumors
INVENTOR(S): Dantzig, Anne Hollins; Grese, Timothy Alan; Norman, Bryan Hurst; Palkowitz, Alan David; Sluka, James Patrick; Starling, James Jacob; Winter, Mark Alan
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 773217	A1	19970514	EP 1996-307955	19961104
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CA 2236543	AA	19970515	CA 1996-2236543	19961104
WO 9717069	A1	19970515	WO 1996-US17533	19961104
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9676028	A1	19970529	AU 1996-76028	19961104
JP 2000500138	T2	20000111	JP 1997-518243	19961104
PRIORITY APPLN. INFO.:			US 1995-6350P P	19951107
			WO 1996-US17533 W	19961104

OTHER SOURCE(S): MARPAT 127:50535
GI



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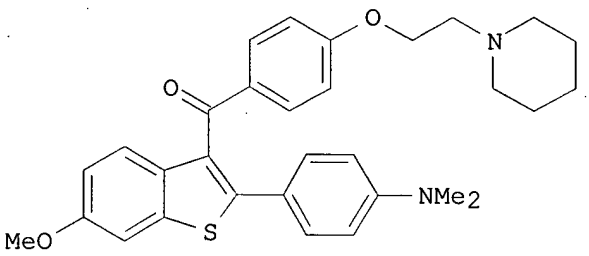

II

AB The invention provides a series of substituted benzo[b]thiophenes I [R1 = OH, halo, H, C1-6 alkyl or alkoxy; R2 = NRaRb; Ra, Rb = H, C1-6 alkyl, CORc, SO2Rc; Rc = C1-6 alkyl, halo, CF3; n = 1-6; R3 = dialkylamino, hexamethyleniminyl, piperazinyl, heptamethyleniminyl, imidazolinyl, piperidinyl, pyrrolidinyl, morpholinyl], useful in reversing multidrug resistance in resistant neoplasms (no data). The invention also provides methods for reversing multidrug resistance in resistant neoplasms by treating mammals with I, or for treating neoplasms in mammals by administering I in combination with **oncolytic** agents. For instance, acylation of 2-(dimethylamino)-6-methoxybenzo[b]thiophene in the 3-position by 4-[2-(piperidin-1-yl)ethoxy]benzoyl chloride hydrochloride (91%), and substitution of the dimethylamino group by 4-(Me2N)C6H4MgBr (63%), gave title compound II.

L42 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:575346 CAPLUS
DOCUMENT NUMBER: 125:265165
TITLE: Reversal of P-glycoprotein-mediated multidrug resistance by a potent cyclopropyldibenzosuberane

modulator, LY335979
AUTHOR(S): Dantzig, Anne H.; Shepard, Robert L.; Law, Kevin L.; Ehlhardt, William J.; Baughman, Todd M.; Bumol, Thomas F.; Starling, James J.
CORPORATE SOURCE: Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285-0424, USA
SOURCE: Cancer Research (1996), 56(18), 4171-4179
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Overexpression of P-glycoprotein (Pgp) by tumors results in multidrug resistance (MDR) to structurally unrelated **oncolytics**. MDR cells may be sensitized to these **oncolytics** when treated with a Pgp modulator. The present study evaluates LY335979 as a modulator both in vivo and in vitro. LY335979 (0.1 μM) fully restored sensitivity to vinblastine, doxorubicin (Dox), etoposide, and **Taxol** in CEMm/VLB100 cells. LY335979 modulated Dox cytotoxicity even when LY335979 (0.5 μM) was removed 24 h prior to the cytotoxicity assay. LY335979 blocked [3H]azidopine photoaffinity labeling of the Mr .apprx.170,000 Pgp in CEM/VLB100 plasma membranes and competitively inhibited equilibrium binding of [3H]vinblastine to Pgp (Ki of .apprx.0.06 μM). Treatment of mice bearing P388/ADR murine leukemia cells with LY335979 in combination with Dox or etoposide gave a significant increase in life span with no apparent alteration of pharmacokinetics. LY335979 also enhanced the antitumor activity of **Taxol** in a MDR human non-small cell lung carcinoma nude mouse xenograft model. Thus, LY335979 is an extremely potent, efficacious modulator that apparently lacks pharmacokinetic interactions with coadministered anticancer drugs and is, therefore, an exciting new agent for clin. evaluation for reversal of Pgp-associated MDR.

L42 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:508520 CAPLUS
DOCUMENT NUMBER: 119:108520
TITLE: Effect of new investigational drug **taxol** on **oncolytic** activity and stimulation of human lymphocytes
AUTHOR(S): Chuang, Linus T.; Lotzova, Eva; Cook, Kenton R.; Cristoforoni, Paolo; Morris, Mitchell; Wharton, J. Taylor
CORPORATE SOURCE: M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Gynecologic Oncology (1993), 49(3), 291-8
CODEN: GYNOA3; ISSN: 0090-8258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Taxol** is a new antineoplastic agent active in the treatment of drug-refractory ovarian and metastatic breast neoplasms. Extensive investigations have been concerned with the effect of **taxol** on a variety of tumor cells, but there is virtually no information about its effect on human lymphocytes. Since lymphocytes, especially natural killer (NK) cells, have been recognized to play an important role in the body's defense against tumors, the effect of **taxol** on the cytotoxicity of naive (unstimulated) peripheral blood mononuclear cells (MNCs) and NK cells as well as on these cells' activation and growth in interleukin-2 (IL-2) cultures were studied. **Taxol** impaired the cytotoxicity of naive MNC and NK cells against the NK-sensitive cell line K-562 and against an ovarian cancer cell line, OV-2774, in a concentration-dependent fashion. The highest impairment was observed after incubation of the effector cells with 10 μg/mL **taxol**. In addition, **taxol** also interfered with the induction of lymphokine-activated cytotoxicity and with lymphocyte growth in IL-2 cultures. However, IL-2 preactivated NK cells displayed substantial levels of cytotoxicity even after **taxol** treatment. These findings, which indicate that treatment with **taxol** should follow rather than precede immunotherapeutic intervention, may by important in planning combined chemo- and immunotherapy strategies for cancer patients.

L42 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:205617 CAPLUS
DOCUMENT NUMBER: 118:205617
TITLE: The ACTH-(4-9) analog, ORG 2766, prevents **taxol**-induced neuropathy in rats
AUTHOR(S): Hamers, Frank P. T.; Pette, Christine; Neijt, Jan P.; Gispen, Willem Hendrik
CORPORATE SOURCE: Med. Fac., Utrecht Univ., Utrecht, 3521 GD, Neth.
SOURCE: European Journal of Pharmacology (1993), 233(1), 177-8
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Taxol** is a novel and promising **oncolytic** agent the use of which is hampered by its neurotoxicity. Here a **taxol**-induced neuropathy in rats and its prevention by the ACTH-(4-9) analog, ORG 2766 is described. A decrease in sensory nerve conduction velocity was seen in **taxol**-treated rats, both with daily injections of small amts. (6 mg/kg per wk) and with weekly injections of higher amts. (9 mg/kg per wk) of **taxol**. Concomitant administration of ORG 2766 completely prevented the occurrence of a neuropathy.

L42 ANSWER 9 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:11790 BIOSIS
DOCUMENT NUMBER: PREV200400015196
TITLE: **Oncolytic** viral therapy for human ovarian cancer using a novel replication-competent herpes simplex virus type I mutant in a mouse model.
AUTHOR(S): Nawa, Akihiro [Reprint Author]; Nozawa, Naoki; Goshima, Fumi; Nagasaka, Tetsuo; Kikkawa, Fumitaka; Niwa, Yoshimitsu; Nakanishi, Toru; Kuzuya, Kazuo; Nishiyama, Yukihiro
CORPORATE SOURCE: Department of Gynecology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan
nawa2000@aichi-cc.jp
SOURCE: Gynecologic Oncology, (October 2003) Vol. 91, No. 1, pp. 81-88. print.
ISSN: 0090-8258 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003

AB Objectives: Attenuated mutant strains of herpes simplex virus (HSV) have been effectively used for treatment of malignant brain tumors. As HSV-1 can infect and lyse a variety of cell types, other malignancies may also benefit from such treatment. We sought to test the feasibility of HSV-1 mutant-mediated gene therapy treatment of ovarian cancer. Methods: We prepared two attenuated mutant HSV-1 strains. An HSV-1 mutant, hrR3, has replaced the gene encoding ribonucleotide reductase (RR) with the lacZ reporter gene. We also developed a new replication-competent HSV-1 mutant, HR522; this virus, expressing the lacZ reporter gene, induces syncytium formation in infected cells. We compared the efficacy of HR522 with, paclitaxel (**Taxol**) and hrR3 in the treatment of nude mice harboring human ovarian cancer cells. We also examined the effect of the prodrug ganciclovir (GCV) on the treatment mediated by these HSVs. Survival was evaluated by Kaplan-Meier method and log-rank test. Results: The survival of mice treated with a high-titer hrR3 (5X107 plaque-forming units (PFU)) was significantly prolonged as compared with the group given paclitaxel ($P<0.0001$, log-rank test). Although the survival of mice treated with high-titer HR522 (5X107 PFU) was not significantly prolonged compared with paclitaxel-treated group ($P=0.212$, log-rank test), GCV markedly enhanced the efficacy of HR522 administration ($P<0.005$, vs paclitaxel, log-rank test). The lacZ gene product, visualized using 5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside (X-gal) histochemistry, was detected in HR522-treated tumors in areas also exhibiting apoptotic changes. Conclusions: These findings indicate that the combination of HR522 and GCV possesses significant therapeutic potential for treatment of ovarian cancer. Such viral therapy offers a novel approach to reductions in the dissemination of ovarian cancer.

L42 ANSWER 10 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on

STN
ACCESSION NUMBER: 2003:238152 BIOSIS
DOCUMENT NUMBER: PREV200300238152
TITLE: Combination of OncoVEX with chemotherapy for cancer treatment.
AUTHOR(S): Hu, J. [Reprint Author]; Hallden, G. [Reprint Author]; Han, Z.; Liu, B.; Robinson, M.; Branston, R.; Coffin, R. S.; Coombes, R. C. [Reprint Author]
CORPORATE SOURCE: Hammersmith Hospital, Cancer Cell Biology Section, Imperial College, Du Cane Road, 6th Floor, MRC Cyclotron Building, London, W12 0NN, UK
SOURCE: Clinical Science (London), (2003) Vol. 104, No. Supplement 49, pp. 31P-32P. print.
Meeting Info.: Spring Meeting of the Medical Research Society. London, UK. February 05, 2003. Medical Research Society.
ISSN: 0143-5221 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003
Last Updated on STN: 14 May 2003

L42 ANSWER 11 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:149260 BIOSIS
DOCUMENT NUMBER: PREV200300149260
TITLE: Combination of OncoVEX with chemotherapy for cancer treatment.
AUTHOR(S): Hu, J. C. C. [Reprint Author]; Han, Z.; Liu, B.; Robinson, M.; Branston, R.; Coombes, R. C.; Coffin, R. S.
CORPORATE SOURCE: BioVex Ltd, 70 Milton Park, Abingdon, OX14 4RX, UK
SOURCE: Cancer Gene Therapy, (January 2003) Vol. 10, No. Supplement 1, pp. S24. print.
Meeting Info.: Eleventh International Conference on Gene Therapy of Cancer. San Diego, CA, USA. December 12-14, 2002.
ISSN: 0929-1903 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2003
Last Updated on STN: 19 Mar 2003

L42 ANSWER 12 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:473377 BIOSIS
DOCUMENT NUMBER: PREV199699202933
TITLE: Reversal of P-glycoprotein-mediated multidrug resistance by a potent cyclopropyldibenzosuberane modulator, LY335979.
AUTHOR(S): Dantzig, Anne H. [Reprint author]; Shepard, Robert L.; Cao, Jin; Law, Kevin L.; Ehlhardt, William J.; Baughman, Todd M.; Bumol, Thomas F.; Starling, James J.
CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Cent., Eli Lilly and Co., Indianapolis, IN 46285-0424, USA
SOURCE: Cancer Research, (1996) Vol. 56, No. 18, pp. 4171-4179.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 1996
Last Updated on STN: 24 Oct 1996
AB Overexpression of P-glycoprotein (Pgp) by tumors results in multidrug resistance (MDR) to structurally unrelated **oncolytics**. MDR cells may be sensitized to these **oncolytics** when treated with a Pgp modulator. The present study evaluates LY335979 as a modulator both in vitro and in vivo. LY335979 (0.1 mu-M) fully restored sensitivity to vinblastine, doxorubicin (Dox), etoposide, and **Taxol** in CEM/VLB-100 cells. LY335979 modulated Dox cytotoxicity even when LY335979 (0.5 mu-M) was removed 24 h prior to the cytotoxicity assay. LY335979

blocked (3H)azidopine photoaffinity labeling of the M-r apprx 170,000 Pgp in CEM/VLB-100 plasma membranes and competitively inhibited equilibrium binding of (3H)vinblastine to Pgp (K-i of apprx 0.06 mu-M). Treatment of mice bearing P388/ADR murine leukemia cells with LY335979 in combination with Dox or etoposide gave a significant increase in life span with no apparent alteration of pharmacokinetics. LY335979 also enhanced the antitumor activity of **Taxol** in a MDR human non-small cell lung carcinoma nude mouse xenograft model. Thus, LY335979 is an extremely potent, efficacious modulator that apparently lacks pharmacokinetic interactions with coadministered anticancer drugs and is, therefore, an exciting new agent for clinical evaluation for reversal of Pgp-associated MDR.

L42 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1993:368432 BIOSIS
DOCUMENT NUMBER: PREV199396054107
TITLE: Effect of new investigational drug **taxol** on **oncolytic** activity and stimulation of human lymphocytes.
AUTHOR(S): Chuang, Linus T. [Reprint author]; Lotzova, Eva [Reprint author]; Cook, Kenton R. [Reprint author]; Cristoforoni, Paolo; Morris, Mitchell; Wharton, J. Taylor
CORPORATE SOURCE: Sect. Natural Immunity, Dep. Gen. Surgery, Univ. Texas M. D. Anderson Cancer Cent., Houston, TX 77030, USA
SOURCE: Gynecologic Oncology, (1993) Vol. 49, No. 3, pp. 291-298. CODEN: GYNOA3. ISSN: 0090-8258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 1993
Last Updated on STN: 8 Aug 1993

AB **Taxol** is a new antineoplastic agent active in the treatment of drug-refractory ovarian and metastatic breast neoplasms. Extensive investigations have been concerned with the effect of **taxol** on a variety of tumor cells, but there is virtually no information about its effect on human lymphocytes. Since lymphocytes, especially natural killer (NK) cells, have been recognized to play an important role in the body's defense against tumors, we studied the effect of **taxol** on the cytotoxicity of naive (unstimulated) peripheral blood mononuclear cells (MNCs) and NK cells as well as on these cells' activation and growth in interleukin-2 (IL-2) cultures. We found that **taxol** impaired the cytotoxicity of naive MNC and NK cells against the NK-sensitive cell line K562 and against an ovarian cancer cell line, OV-2774, in a concentration-dependent fashion. The highest impairment was observed after incubation of the effector cells with 10 mu-g/ml **taxol**. In addition, **taxol** also interfered with the induction of lymphokine-activated cytotoxicity and with lymphocyte growth in IL-2 cultures. However, IL-2 preactivated NK cells displayed substantial levels of cytotoxicity even after **taxol** treatment. These findings, which indicate that treatment with **taxol** should follow rather than precede immunotherapeutic intervention, may be important in planning combined chemo- and immunotherapy strategies for cancer patients.

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AB **Taxol** is a novel and promising **oncolytic** agent the use of which is hampered by its neurotoxicity. We now describe a **taxol**-induced neuropathy in rats and its prevention by the adrenocorticotropic hormone-(4-9)(ACTH-(4-9)) analog, ORG 2766. A decrease in sensory nerve conduction velocity was seen in **taxol** -treated rats, both with daily injections of small amounts (6 mg/kg per week) and with weekly injections of higher amounts (9 mg/kg per week) of **taxol**. Concomitant administration of ORG 2766 completely prevented the occurrence of a neuropathy.

subjects and other mammals, each unit containing a predetermined quantity of reovirus calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

It is contemplated that the present invention may be combined with other tumor therapies such as radiation therapy or surgery.

In addition, the present invention provides a method for preventing a neoplasm from developing drug resistance. Progressive drug resistance is developed by treating a neoplasm with a drug which kills the drug sensitive cells within the neoplasm, thereby selecting the drug resistant cells. Upon expansion of the drug resistant cells, the neoplasm manifests the phenotype of drug resistance. Accordingly, reovirus can be used to sensitize the neoplasm at the onset of the course of chemotherapy such that all cells are killed or inhibited, including the drug resistant cells. Therefore, the neoplasm so treated would have no opportunity to develop drug resistance.

A cell which is resistant to one drug is often resistant to another drug due to the phenomenon of multiple drug resistance. Therefore, reovirus is preferably administered to a neoplasm which has not been treated with any chemotherapeutic agent in order to prevent the development of drug resistance. Once drug resistance has developed, however, reovirus can still be used to sensitize the drug resistant cells and increase the efficacy and selectivity of chemotherapy, as well as directly killing the neoplastic cells by oncolysis.

As noted above, we believe that reovirus sensitizes neoplastic cells to chemotherapeutic agents by inhibiting host cell protein synthesis or inducing apoptosis. Therefore, it is contemplated that other viruses can also be used in the same manner as reovirus. In particular, the viruses that selectively infect neoplastic cells are preferred. These viruses include, but are not limited to, modified adenovirus, modified HSV,